Paper No. 20

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MAY TOM-MOY, THOMAS P. DOHERTY,
RICHARD L. BAER, and DARLENE J. SPIRA-SOLOMON

Appeal No. 2001-2521
Application No. 08/738,464

ON BRIEF

Before WINTERS, WILLIAM F. SMITH, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-14, all of the claims in the application. Claim 1 is representative and reads as follows:

1. A method for determining the presence or quantity of a preselected analyte in a flowing liquid stream which contains or is suspected of containing the analyte, which method comprises:

(a) continuously contacting the flowing liquid stream with an on-line system which comprises:

(i) a piezoelectric surface wave sample device comprising a receptor layer attached to the surface thereof wherein the receptor layer consists

essentially of a receptor species complementary to the analyte and which device generates data relating to the mass change on the surface of the device arising from contacting the device with the flowing liquid stream; and

(ii) a piezoelectric surface wave reference device comprising a receptor layer having little or no affinity for the analyte and which generates data as to the interference arising from contacting the device with the flowing liquid stream;

(b) continuously obtaining data from both the sample and reference devices; and

(c) continuously, and contemporaneously with step (a), determining the presence, quantity, or both the presence and quantity of the analyte in the liquid sample.

The examiner relies on the following references:

DeFord et al. (DeFord)	4,283,201	Aug. 11, 1981
Issachar	5,156,972	Oct. 20, 1992
Ghazarossian et al. (Ghazarossian)	5,180,828	Jan. 19, 1993
Ligler et al. (Ligler)	5,183,740	Feb. 02, 1993
Myerholtz et al. (Myerholtz)	5,306,644	Apr. 26, 1994

The claims stand rejected under 35 U.S.C. § 103 as obvious in view of the prior art, as follows:

- Claims 1-14 in view of Issachar;
- Claims 1-7, 13, and 14 in view of Myerholtz and DeFord;
- Claims 8-12 in view of Myerholtz, DeFord, and Ghazarossian;
- Claims 1-7 and 13 in view of Myerholtz and Ligler; and
- Claims 8-12 in view of Myerholtz, Ligler, and Ghazarossian.

We reverse all of these rejections.

Background

"Mass biosensors have been used to measure microquantities of biological materials, and involve the use of a modified surface which selectively binds a particular component. As explained in . . . U.S. Patent No. 5,306,644 to Myerhol[t]z et al. . . . a preferred type of mass biosensor uses a piezoelectric crystal as an acoustic waveguide. These sensors operate on the principle that changes in the amount of mass attached to their surface cause shifts in the resonant frequency." Specification, pages 3-4.

"For example, and as explained in [Myerholtz], piezoelectric surface wave devices have been used to measure the concentration of a specific antigen in solution using a conventional assay format, as follows. The mass-sensitive surface of the device is coated with a receptor layer which contains the antibody corresponding to the antigen, thereby forming a sample-sensing device. A reference device is also used which does not contain the antibody in the receptor layer. The devices are then exposed to a sample solution, and antigen present in the solution will bind to the receptor layer of the sample-sensing device, thereby increasing the mass loading of the surface." Id., page 4.

"The present invention . . . employs a piezoelectric mass biosensor for continuous on-line monitoring of preselected analytes in a flowing liquid stream." Id., page 5. "One of the main advantages of using an STW [surface transverse wave] biosensor for liquid chromatography detection is the ability to make continuous measurements. . . . For example, as the chromatographic run takes place, eluant passes from the column to the sensor. When the target analyte is

present, the sensor will generate a signal that is the integral of the analyte concentration over time. By taking the derivative of the signal one can generate a signal that is related to the amount of compound flowing over the sensor as a function of time." Id., pages 24-25.

Discussion

Claim 1 is directed to a method for detecting or quantitating an analyte in a flowing liquid stream, comprising continuously contacting the liquid stream with a detector comprising a "piezoelectric surface wave sample device" and a "piezoelectric surface wave reference device," continuously obtaining data from both devices, and continuously determining the presence and/or quantity of analyte present in the liquid stream.[1] The examiner rejected claim 1 as obvious over Issachar alone, or over Myerholtz in combination with either DeFord or Ligler.

1. Issachar

The examiner characterized Issachar as disclosing "an analyte specific chemical sensor for determining an analyte in a test medium, which comprises a sensing surface coated with reversible competitive recognition units (RCRUs) which in turn contain at least one receptor and one ligand[,] one of which components is an analyte analog." Paper No. 12, mailed June 24, 1997, page 4. The examiner acknowledged that "the reference does not teach the specific use of, or exemplify, a piezoelectric devi[c]e for continuous measurement of an

[1] For reasons that will become apparent, we need not separately consider the dependent claims.

analyte in a sample." Id., page 5. He nevertheless concluded that

> it would have been obvious to one having ordinary skill in the art at the time of invention to have detected or measured analyte concentration in a sample by continuously and contemporaneously measuring the physicochemical changes occurring in a biosensor coated with a binding partner for the analyte . . . as a result of the reaction of the analyte with the binding partner, as suggested by the reference, and use a piezoelectric biosensor as the physicochemical devi[c]e because the reference teaches that any suitable physicochemical measurement may be employed and includes piezoelectric properties among them.

Id.

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). The obviousness analysis must be based on the claimed "subject matter as a whole." 35 U.S.C. § 103(a). That is, every limitation must be considered. See In re Lowry, 32 F.3d 1579, 1582, 32 USPQ2d 1031, 1034 (Fed. Cir. 1994) ("The Patent and Trademark Office (PTO) must consider all claim limitations when determining patentability of an invention over the prior art.").

In this case, we agree with Appellants that Issachar does not support a prima facie case of obviousness. The claimed method requires use of a system comprising a "sample device" and a "reference device." The examiner has not shown that these limitations would have been suggested by Issachar. The examiner responded to Appellants' argument on this point as follows:

> Applicants also argue that the reference does not teach the employment of [a] second sensor comprising a receptor having little

> or no affinity for the analyte of interest. However, such second sensor would really be like a control or a blank which would correct for any non-specific interaction of the sensor surface with an analyte. Nothing unobvious is seen i[n] the use of a control sensor for correcting non-specific interactions between the sensor and the analyte.

Examiner's Answer, pages 10-11.

The examiner's conclusory statement that "nothing unobvious is seen in" the use of a second (reference) sensor is inadequate to show that such a sensor would have been suggested by the prior art. "It is fundamental that rejections under 35 U.S.C. § 103 must be based on evidence comprehended by the language of that section," In re Grasselli, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983), not on unsupported assertions of what would or would not have been obvious. The rejection based on Issachar is reversed.

2. Myerholtz and DeFord or Ligler

The examiner also rejected claim 1 as obvious over Myerholtz in combination with either DeFord or Ligler. The examiner characterized Myerholtz as teaching a system for measuring analytes in liquid samples. See Paper No. 2, mailed August 21, 1995, page 5. The examiner noted the Myerholtz's system is in many ways similar to that used in the instantly claimed method, but acknowledged that it "differ[s] from the instant invention in that the [prior art] measurement system is configured for individual liquid samples rather than a continuous liquid stream." Id.

The examiner relied on DeFord or Ligler to make up this deficiency in the primary reference. He characterized DeFord as teaching "a column

chromatography system for analytes comprising a sample valve, a chromatographic column, an elution buffer chamber and pump for eluting the column, and a double celled detector device for detecting analyte in a continuous stream of eluate." Id., pages 5-6 (reference numerals omitted). He concluded that

> [it] would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the piezoelectric detector of Myerholtz in the automated chromatographic system taught by DeFord et al. because detection of the analyte directly in the effluent stream as it comes out of the column saves the user the labor of adding individual column fractions to the piezoelectric detector.

Id., page 6.

We do not agree that the claimed invention would have been obvious based on Myerholtz and DeFord. First, the examiner's characterization of DeFord as teaching a "column chromatography system" is somewhat misleading. A "column chromatography system" is used to separate and purify components of a mixture. See, e.g., the instant specification, page 1: "Processing biological materials often involves the use of liquid chromatography to separate and harvest a cellular product. . . . Typically, extracting the product of interest is accomplished using a series of chromatographic separations" (emphasis added).

While the system disclosed by DeFord can include a chromatographic column, the column is not used to perform chromatography; i.e., it is not used to separate components of a mixture. DeFord states that the "column" in the disclosed device is used to effect sample titration. See, e.g., column 1, lines 8-14: "Sample titration is effected utilizing a holding zone or column, e.g., a

chromatographic column[,] and a titrant . . . with the holding zone or column functioning to retain a known or metered and injected sample for a time sufficient to enable quantitative reaction thereof with the titrant."

The examiner's characterization of DeFord's system as a "automated chromatographic system" that generates "individual column fractions" is also not accurate. DeFord characterizes the disclosed "method and apparatus [as] providing continually repeated or sequential on-line chemical analyses." Column 1, line 6-8. This is accomplished by "utilizing a holding zone or column, e.g., a chromatographic column[,] and a titrant . . . with the holding zone or column functioning to retain a known or metered and injected sample for a time sufficient to enable quantitative reaction thereof with the titrant flowing through said column continuously except when the injected sample, in effect sharply defined slug, is flowing into and reacting in said zone, thus creating a titrant 'vacancy' in the zone or column effluent which is detected and can be recorded."

The examiner's characterization of DeFord as teaching a chromatographic method was the basis on which he asserted it would have been obvious to combine DeFord and Myerholtz. Since, as we have discussed, DeFord does not teach a chromatographic method, we cannot agree with the examiner that it would have been obvious to combine DeFord and Myerholtz in order to "sav[e] the user the labor of adding individual column fractions to the piezoelectric detector." The rejections based on Myerholtz and DeFord is reversed.

The examiner also rejected claim 1 as obvious over Myerholtz and Ligler. He characterized Ligler as teaching a chromatographic system comprising, inter

alia, "a detection means for monitoring the column eluate for analyte comprised of an analyte detection cell . . . and a reference cell." Paper No. 2, page 8. He concluded that

> [it] would have been obvious to a person of ordinary skill in the art to substitute the piezoelectric detector of Myerholtz in the automated chromatographic system taught by Ligler et al. because Ligler et al[.] teach the importance of being able to detect analyte in real time without the need for testing individual samples (column 4, lines 5-18; column 6, lines 3-6) and the sensor taught by Myerholtz et al., in which the liquid stream flows in parallel over the sample and reference devices in order to synchronize their exposure cycles . . . would give real time measurements of analyte concentration.

Id.

When determining obviousness, "the prior art as a whole must be considered. The teachings are to be viewed as they would have been viewed by one of ordinary skill." In re Hedges, 783 F.2d 1038, 1041, 228 USPQ 685, 687 (Fed. Cir. 1986). "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." Id.

In this case, we agree with Appellants that the cited references, when considered in their entirety, would not have suggested the instantly claimed method. The method disclosed by Ligler is based on displacement of labeled analyte by unlabeled analyte that is present in the sample. See column 4, lines 19-27, and Figure 2. The detector that is used in the system therefore must detect not just analyte, but labeled analyte. See column 4, lines 19-27: "[The] objects of the invention are accomplished by a method of detecting a target

moiety comprising the steps of . . . (e) detecting the displaced labelled antigen with a detector for the label" (emphasis added). See also column 4, lines 51-58:

> The detection apparatus will be different for each type of label. When the label is a radiolabel, the detector contains, at least, a radiation sensor to detect and display the quantity of radiation detected. If a fluorescent label is used, the detection apparatus contains at least a light source for exciting the fluorophore-labelled antigens to fluoresce and a reading means for detecting and displaying the quantity of fluorescent light generated.

Thus, Ligler suggests that the detector used in the disclosed chromatographic system must be capable of detecting a label that is attached to an analyte. Myerholtz's system, by contrast, detects the analyte itself. Myerholtz points out that the disclosed system does not require any labeling of the analyte. See column 18, lines 12-14: "[T]here is no need to derivatize the sample or related reagent solutions with radioactive, fluorescent, or chemiluminescent labels."

The examiner has not adequately explained what would have led a skilled artisan to combine a chromatographic system that depends on detection of a label (Ligler) with a detection system that is incapable of detecting a label (Myerholtz). Since the examiner has not shown that a skilled artisan would have been led to combine the teachings of Ligler and Myerholtz, the references do not support a prima facie case of obviousness. The rejections based on Myerholtz and Ligler are reversed.

Summary

The references relied on by the examiner either do not suggest all of the limitations of the instant claims, or do not suggest combining those limitations. They therefore do not support a prima facie case of obviousness under 35 U.S.C. § 103, and all of the rejections on appeal are reversed.

REVERSED

Sherman D. Winters Administrative Patent Judge	))))) BOARD OF PATENT
William F. Smith Administrative Patent Judge	)) APPEALS AND)) INTERFERENCES
Eric Grimes Administrative Patent Judge	))

EG/dym

Agilent Technologies, Inc.
Intellectual Property Administration, LE
P.O. Box 7599
M/S DL429
Loveland, CO 80537-0599